Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 34-35, 38-39, 41-42, 44, 46, 52, and 55-66 are pending in the application, with claims 1, 34, 52, 58, and 66 being the independent claims. Claims 2-33, 36-37, 40, 43, 45, 47-51, and 54 were previously sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claim 53 is herewith sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue any of the canceled subject matter in related applications. Claims 1, 34, 52, 58, and 66 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Support for the amendment to claim 52 is found, *inter alia*, in previously pending claim 53 and in the specification as filed at page 3, lines 21-26.

Support for the amendment to claim 1 is found, *inter alia*, in previously presented claim 56 and in the specification as filed at page 16, lines 10-17.

Support for the amendment to claims 1, 34, and 58 is found, *inter alia*, in the specification as filed at page 5, lines 26-32.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Claim Rejections under 35 U.S.C. § 112, First Paragraph, New Matter

A. "liposome-encapsulated cytotoxin"

Claims 58-66 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly including new matter based on the language "liposome-encapsulated cytotoxin." The Examiner asserts that the specification only offers support for the species liposome-encapsulated doxorubicin. Office Action at pages 3-4. Applicants respectfully traverse.

Current law does not require Applicants to recite more than one species of a well-known genus in order to demonstrate possession of a genus. A representative number of species is unnecessary when "the claim terms at issue...are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) ("*Amgen*").

In *Amgen,* the claimed methods included, *inter alia*, the step of "growing...vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence..." *Id.* at 1322. Also at issue were dependent claims that specified that the cells were mammalian cells. *Id.* The defendants asserted that the claims lacked adequate written description, alleging that Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells. *Id.* at 1331. The Federal Circuit disagreed, maintaining that written description is sufficient when the subject matter in question is well known and fully appreciated by persons of ordinary skill in the art. *Id.* at 1332 (internal citations omitted). The Federal Circuit refused to apply the "representative number of species" test to the terms "vertebrate cells" and "mammalian cells" because those of ordinary skill in the art would readily comprehend the members

of the genus. *Id.* Further, the court concluded that the claims at issue were adequately described, even though the specification described only two species within the genus vertebrate or mammalian cells. *Id.*

As with the vertebrate and mammalian cells in *Amgen*, "liposome-encapsulated cytotoxins" were "not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend... ." *Id.* 314 F.3d 1313, 1332 (Fed. Cir. 2003)(emphasis added). As recognized by the Examiner, "the Art of record demonstrates a knowledge that liposome-encapsulated cytotoxic drugs will target and kill kupffer cells when administered through specific routes... ." Office Action at page 4 (emphasis added); *see also*, previous Office Action at page 9. Furthermore, Applicants' Specification discloses doxorubicin as an example of an agent that reduces Kupffer cell levels (*See* Specification, for example, at page 3, lines 27-30), and doxorubicin was a well-known cytotoxin at the time of Applicants' filing (*See*, for example, Daemen, *et al.*, *Int. J. Cancer 61*: 716-721 (1995)(as submitted in the Information Disclosure Statement filed on February 27, 2004)). In view of knowledge in the art concerning killing of Kupffer cells by liposome-encapsulated cytotoxins as recognized by the Examiner, in view of doxorubicin's well-known action as a cytotoxin, and based on Applicant's teaching that liposome-encapsulated doxorubicin is an *example* of an agent that reduces Kupffer cell levels, one of ordinary skill in the art would have understood that Applicants were in possession of liposome-encapsulated cytotoxins in addition to doxorubicin for reduction of Kupffer cell levels. Given the latter, Applicant has fulfilled the requirement of 35 U.S.C. § 112, First Paragraph, Written Description as defined by current law in demonstrating possession of "liposome-encapsulated cytotoxins."

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the new matter rejection.

B. "a promoter which functions in hepatocytes"

Claims 1, 34-35, 38-39, 41-42, 44, 46, 52-53, and 55-56 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly including new matter based on the language "a promoter which functions in hepatocytes." Office Action at page 5. Applicants respectfully traverse the rejection.

The Examiner asserts that the specification offers no support for a generic promoter functional in hepatocytes other than a single paragraph reciting tissue-specific promoters. Office Action at page 5. For clarification, Applicants note that the claims do not require a tissue-specific promoter, *i.e.*, a promoter functional only in hepatocytes. As would be understood by one of ordinary skill in the art, a promoter that is *functional* in hepatocytes is not limited to a promoter that is *specific* to hepatocytes. A promoter that is functional in hepatocytes could also be functional in other tissues.

As previously recognized by the Examiner, the claims are enabled for "expression control elements for expression in hepatocytes." Previous Office Action at page 9. Promoters were well-known in the art at Applicants' filing date and one of ordinary skill in the art would have been readily able to select promoters for expression in hepatocytes based on such knowledge. In terms of the written description requirement, current law does not require Applicants to describe or recite specific promoter sequences in order to demonstrate possession of such sequences. *See Capon v. Eshhar* 418 F.3d 1349, 1358 (Fed. Cir. 2005) ("*Capon*") and *Falko-Gunter Falkner v. Inglis* 448 F.3d 1357, 1367-1368 (Fed. Cir. 2006) ("*Falkner*").

In *Capon*, the claimed methods included, *inter alia*, the production of chimeric genes for providing cells of the immune system with cell-surface antibodies for infiltration of disease sites. *Id.* at 1351. The Board of Patent Appeals and Interferences held that the claims were invalid, asserting that the specifications at issue failed to provide written description regarding "structure, formula, chemical name or physical properties" for the full scope of the claimed chimeric DNA or encoded proteins. *Id.* at 1354. The Federal Circuit disagreed, stating that written description requirements vary based on the invention at issue in light of "the scientific and technologic knowledge already in existence" and that no descriptive substance would be added by requiring written description of known sequences. *Id.* at 1357-1358.

Falkner involved an interference between Falkner and Inglis. 448 F.3d 1357 (Fed. Cir. 2006). At issue was whether Inglis' priority applications demonstrated possession of subject matter relating to a vaccine comprising a poxvirus in which an essential gene is inactivated. *Id.* at 1360. Falkner argued, *inter alia*, that Inglis' priority applications did not identify any essential poxvirus genes and thus lacked written description. *Id.* at 1362. The Federal Circuit affirmed the holding of the Board of Patent Appeals and Interferences that possession was in fact demonstrated. *Id.* at 1368. The Federal Circuit noted that essential poxvirus genes for poxvirus were well-known in the art such that one of ordinary skill in the art would be readily able to choose an essential gene. *Id.* at 1336 and 1338. The Federal Circuit reiterated its holding in *Capon*, further stating that

> ...a requirement that patentees recite known DNA structures... would serve no goal of the written description requirement... Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification...

> Accordingly, we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences...satisfaction of the written description requirement does not require either the recitation or incorporation by reference...of such genes and sequences.

Id. (emphasis added).

In *Falkner*, possession of an "essential viral gene" for poxvirus was satisfied based on well-known sequences in the art even though the specification provided no examples of such genes. Similarly, possession of "a promoter, which functions in hepatocytes" requires no actual examples or disclosure in Applicants' specification given well-known promoters in the art. Despite no requirement to do so, Applicants' Specification clearly *does* teach promoters functional in hepatocytes, including promoters such as the cytomegalovirus (CMV) promoter listed in the bridging paragraph of pages 9-10, and references cited therein, and in the Examples demonstrating expression in the liver. *Id.* As such, Applicants meet the requirements of current law for satisfying possession and are not required to specifically list additional promoter sequences that could have readily been selected by one of ordinary skill in the art for expression in hepatocytes.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the new matter rejection.

II. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 34-39, 41-44, 46, and 52-54 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 36-37, 43, and 54 were previously canceled.

A. Increasing the levels of a therapeutic gene product in a tissue other than liver

The Examiner asserts that the claims allegedly lack enablement for increased expression in non-liver tissues, stating that by "simply providing a generalized increased expression in the subject, it is clear that the claims are specifically meant to encompass increased expression in any tissue." Office Action at pages 8-9. It is Applicant's understanding that claims 1, 34, and 58, reciting methods for increasing the levels of a therapeutic gene product in a subject, are the independent claims at issue.

Purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended claims 1, 34, and 58 to recite methods where the levels of a therapeutic gene product "are increased in hepatocytes" by administration of the agent.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

B. Conjugation of Therapeutic Viral Vectors and Agents

The Examiner asserts that claims reciting concurrent administration of a first viral vector and an agent allegedly lack enablement in the absence of language stating that the viral vector and the agent are not conjugated given the presence of such language in claim 52. Office Action at page 9. It is Applicant's understanding that claims 1, 58, and 66 are the independent claims at issue.

Purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended claims 1, 58, and 66 to recite that "said first viral vector and said agent are not conjugated."

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

III. Claim Rejections under 35 U.S.C. § 102 Based on Wilson et al.

Claims 52, 53, and 55 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. 6,001,557 (hereinafter, 'Wilson *et al.*'). Wilson teaches co-transfection *in vitro* of a shuttle vector encoding the therapeutic transgene and a helper virus. *Id.* at col. 5, lines 32-49, and Example 3. The Examiner asserts that claims 52 and 55 are allegedly anticipated since the shuttle and helper virus are in water, and that claim 53 is allegedly anticipated given that the helper virus allows for packaging. Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

In order to anticipate a claim, a single reference must teach and enable each and every element of that claim. *See* M.P.E.P. § 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), and *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909, 107 S. Ct. 2490 (1987). Claims 52 and 55 as amended require that the first and second viral vectors of the pharmaceutical composition "are provided in viral particles." Wilson *et al.* does not teach a pharmaceutical composition comprising first and second viral vectors provided in viral particles. While the helper virus of Wilson *et al.* may allow for production of a packaged virus *after* transfection, the helper and shuttle viruses themselves are not individually in particle form when they are administered to the cells. *Id.* at col. 13, lines 45-54, and Example 3. Furthermore, while the helper and shuttle viruses of Wilson *et al.* are co-

transfected, they are not co-administered as a single composition as is clear from the description at col. 13, lines 51-54 (stating that "...helper virus is used to infect cells...which are then **subsequently** transfected with...shuttle vector...") and Example 3. *Id.* In contrast, the first and second viral vectors of claim 52 (1) are each individually packaged as viral particles in the composition, and (2) are co-administered. As such, Wilson *et al.* fails to teach the compositions of claims 52 and 55.

Given the failure of Wilson *et al.* to disclose all of the elements of claims 52 and 55, Applicants respectfully request that the Examiner reconsider and withdraw the novelty rejection.

IV. Claim Rejections under 35 U.S.C. § 102 Based on Graham et al.

Claims 1, 38, 43, and 52-54 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. 6,730,507 (hereinafter, 'Graham *et al.*'). Claims 43 and 54 were previously canceled. Claims 1, 38, and 52-54 are pending. Graham *et al.* teaches sequential administration of a second viral serotype containing a transgene three months after a first viral seroptype containing a transgene. *Id.* at col. 3, lines 31-35, and col. 5, lines 39-41. The Examiner asserts that the claims are allegedly anticipated since the serotypes may contain different transgenes. Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

Claims 1 and 38 as amended require that the second viral vector agent is administered "less than 24 hours prior to or concurrently with" administration of the first viral vector. Graham *et al.* does not teach administration of a second viral vector that does not contain the therapeutic nucleic acid less than 24 hours prior to or concurrently

with administration of the first viral vector. Instead, Graham *et al.* teaches administration of an adenovirus of a different serotype 90 days (3 months) after administration of a first adenovirus. *Id.* at col. 3, lines 31-35, and col. 5, lines 39-41. As such, Graham *et al.* does not teach the methods of claims 1 and 38.

Claim 52 as amended requires that the first and second viral vectors of the pharmaceutical composition "are provided in viral particles." Graham *et al.* does not teach a pharmaceutical composition comprising first and second viral vectors provided in viral particles. Instead, Graham *et al.* teaches separate administration of an adenovirus of a different serotype 90 days (3 months) after administration of a first adenovirus. *Id.* at col. 3, lines 31-35, and col. 5, lines 39-41. At best, Graham *et al.* teaches co-transfection of a helper-dependent adenovirus vector encoding a transgene and a helper virus for subsequent packaging of the helper-dependent adenovirus vector. *Id.* at col. 6, lines 21-27. Graham *et al.* does not teach co-administration of two individually packaged viruses. As such, Graham *et al.* does not teach the composition of claim 52.

Given the failure of Graham *et al.* to disclose all of the elements of claim 52, Applicants respectfully request that the Examiner reconsider and withdraw the novelty rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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